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Association of Indoor Nitrogen Dioxide with Respiratory Symptoms and Pulmonary Function in Children

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The effect of indoor nitrogen dioxide on the cumulative incidence of respiratory symptoms and pulmonary function level was studied in a cohort of 1,567 white children aged 7–11 years examined in six US cities from 1983 through 1988. Week-long measurements of nitrogen dioxide were obtained at three indoor locations over 2 consecutive weeks in both the winter and the summer months. The household annual average nitrogen dioxide concentration was modeled as a continuous variable and as four ordered categories. Multiple logistic regression analysis of symptom reports from a questionnaire administered after indoor monitoring showed that a 15-ppb increase in the household annual nitrogen dioxide mean was associated with an increased cumulative incidence of lower respiratory symptoms (odds ratio (OR) = 1.4, 95% confidence interval (95% CI) 1.1–1.7). The response variable indicated the report of one or more of the following symptoms: attacks of shortness of breath with wheeze, chronic wheeze, chronic cough, chronic phlegm, or bronchitis. Girls showed a stronger association (OR = 1.7, 95% CI 1.3–2.2) than did boys (OR = 1.2, 95% CI 0.9–1.5). An analysis of pulmonary function measurements showed no consistent effect of nitrogen dioxide. These results are consistent with earlier reports based on categorical indicators of household nitrogen dioxide sources and provide a more specific association with nitrogen dioxide as measured in children's homes. *Am J Epidemiol* 1991;134:204–19.

air pollutants; child; household articles; lung; nitrogen dioxide; respiratory function tests; respiratory tract diseases

Nitrogen dioxide is a by-product of high-temperature combustion in air. While most outdoor locations have an annual mean below the National Ambient Air Quality Standard of 100 $\mu g/m^3$ (53 ppb) (1), the concentration of nitrogen dioxide may exceed this level in homes with unvented gas- or kerosene-fueled appliances (2). Previously

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Abbreviations: 95 percent CI, 95 percent confidence interval; $FEF_{25-75\%}$, forced expiratory flow between 25 percent and 75 percent of forced vital capacity; $FEV_{0.75}$, forced expiratory volume in three-fourths of a second; $FEV_{1.0}$, forced expiratory volume in 1 second; FVC, forced vital capacity; ln, natural logarithm; OR, odds ratio; $PM_{2.5}$, particulates with a mean aerodynamic diameter less than 2.5 μm.

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published results from the Harvard Six Cities Study (3, 4) have described the associations between respiratory symptoms and pulmonary function in two cohorts of preadolescent children with indicators of indoor pollution sources determined from questionnaires: parental smoking, gas stoves, and kerosene heaters. While evidence of increased respiratory symptoms and lower lung function has been reported for passive smoke exposure, the association with nitrogen dioxide sources has been less consistent. Only reported respiratory illness before the age of 2 years was positively associated with the presence of nitrogen dioxide sources in two cohorts of children in the Harvard Six Cities Study. Some measures of pulmonary function were also depressed for children with unvented gas or kerosene appliances. The misclassification of exposure potentially could be diluting any effect of nitrogen dioxide sources in these studies (5). In this paper, we present results from a study of a subset of the second cohort of children enrolled in the Harvard Six Cities Study, in which each child's residential exposure to nitrogen dioxide was directly measured by indoor monitoring.

MATERIALS AND METHODS

Study population

The study population was drawn from a cohort of 6,273 children from six different communities: Watertown, Massachusetts; Kingston and Harriman, Tennessee; the Carondolet area of St. Louis, Missouri; Steubenville, Ohio; Portage, Wisconsin, and surrounding communities; and a random sample of schools in Topeka, Kansas. A parent-completed respiratory symptom questionnaire and a pulmonary function examination were initially administered in a staggered scheme across cities between September 1983 and June 1986. The following year in each city, a second questionnaire and pulmonary function examination were administered to all of these children who were still living in these communities. Between 1 year and 18 months later in the fall, the parents received a third health questionnaire. All children in specific grades of public and private elementary schools within the geographically defined study areas were enrolled so as to obtain a sample of about 1,000 children in each city: the third and fourth grades in St. Louis and Topeka, second through fourth grade in Steubenville, and second through fifth grade in Watertown, Kingston, and Portage.

In each city, a stratified one-third random sample of the first questionnaire respondents was solicited to participate in a comprehensive program of indoor air quality measurements. These children also kept a diary of respiratory symptoms (results not presented here). The initial stratified sampling strategy was to obtain 70 percent smoking households and 70 percent households with a major nitrogen dioxide source (gas cooking stove or kerosene heater) as reported on the first respiratory symptom questionnaire. The achieved proportions, 58 percent smoking households and 48 percent households with a major nitrogen dioxide source, were lower than planned because of geographic differences in gas stove utilization and smoking. The sampling strategy minimized the association between nitrogen dioxide and passive smoking exposures by ensuring essentially equal proportions of current smoking homes in each nitrogen dioxide exposure stratum.

Indoor air quality measurements

Indoor air measurements were made in each participating household in two consecutive 1-week sampling periods in winter (mid-November through March) and in summer (mid-May through September) (6). The present analysis will report associations between respiratory health and indoor nitrogen dioxide with indoor respirable particle treated as a covariate. An integrated nitrogen dioxide sample was collected each sampling week using Palmes' passive diffusion tubes (7, 8) in the kitchen, activity room, and child's bedroom. In the first three cities (Watertown, Kingston, and St. Louis), two

separate 1-week samples were collected, while a single 2-week measurement for each season was collected in Steubenville, Portage, and Topeka. Preassembled monitoring kits were placed in a sample of homes each week and returned to the central laboratory for analysis. The monitoring kits included randomly assigned replicates (5 percent) and field blanks (5 percent). A few samples (<0.5 percent) were voided for errors in sampling or analysis. In addition, two samples with measurements less than field blanks were assumed to have not been properly exposed. The passive sampling device functioned continuously throughout the sampling period. Homes without at least one valid measurement for both nitrogen dioxide and respirable particulates ($n = 26$) were excluded, leaving 1,844 children in the subsample. For children with at least one measurement, a value for any one missing season was imputed for either the winter ($n = 42$) or the summer ($n = 204$) (9) (see Appendix). An annual nitrogen dioxide average was then calculated as the geometric mean of the two seasonal estimates for each location, and a household annual nitrogen dioxide average was calculated as the arithmetic mean of the annual nitrogen dioxide averages for the three locations. Respirable particulates less than 2.5 μm in diameter ($PM_{2.5}$) were measured by a Harvard aerosol impactor (10), which ran continuously in the activity room except for 8 hours each weekday when the child was normally in school.

Racial, age, and completeness restrictions

The analysis was restricted to white children between the ages of 7 and 11 at the first examination with complete information on a series of covariates: parental education and respiratory illnesses, family size and composition, number of rooms, and maternal smoking during pregnancy. The racial restriction excluded 149 children (8.1 percent), age excluded a further 19 children (1.1 percent), and the completeness of data excluded a final 109 children (6.5 percent), for a final sample size of 1,567 children (figure 1).

The composition of the eligible cohort varied slightly with each questionnaire. Since the indoor measurements were obtained during the final year, the analysis was restricted to those earlier questionnaires for which there were not subsequently 1) a change in residence, 2) a change in type of cooking stove, or 3) a change in the family smoking status (smoking vs. nonsmoking). The number of completed questionnaires for this sample over the course of the study was 1,115 for the first questionnaire, 1,221 for the second, and 1,286 for the third. The response rate for the third questionnaire was lower in homes with a nitrogen dioxide source (77 percent), primarily because of a poor overall response rate for a mail distribution of the third questionnaire in Watertown (53 percent). In the other cities, the questionnaires were handled through the schools, and the response rate for the third questionnaire in these five cities was accept-

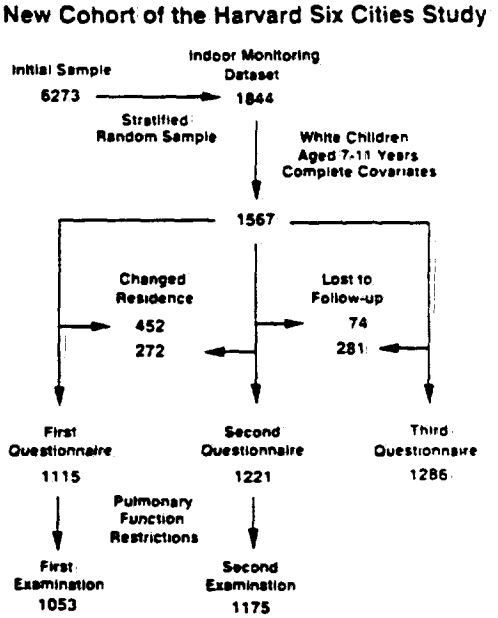

FIGURE 1. Schematic representation of the selection process and sample attrition, indoor monitoring dataset, Harvard Six Cities Study, 1983–1988. Changed residence implies either movement to a new residence or a major change in indoor pollutant sources

able in both homes with a nitrogen dioxide source (84 percent) and homes without a nitrogen dioxide source (90 percent).

Cumulative incidence of respiratory symptoms

Each questionnaire followed a standard format (11) and solicited responses to a series of questions on respiratory symptom prevalence during the year preceding the questionnaire. The third questionnaire was administered in the fall following the completion of the indoor air quality measurements and provides symptom information for the year during which the measurements were taken. A single binary variable was created that indicated the occurrence during the prior year of one or more of the following five lower respiratory symptoms: shortness of breath with wheezing, persistent wheeze, chronic cough, chronic phlegm, and bronchitis. Asthmatic status was based solely on a parental report of a physician's diagnosis and not on the presence of asthmatic symptoms. Hay fever and earache were reported separately. The chest illness and other illness variables reflect a restriction of the child's normal activities for 3 or more days. The other illness question excluded chest illness, but may have included upper respiratory illnesses.

Pulmonary function measurements

Measurements of pulmonary function have been discussed previously as an indicator of the effects of air pollutants (12). The pulmonary function measurements were conducted by trained spirometry field teams in the child's school using a recording survey spirometer (Warren E. Collins, Inc., Braintree, Massachusetts). After the child's weight and height in stocking feet were measured, each child performed at least five but not more than eight forced expiratory maneuvers while sitting with free mobility and without a noseclip. Unacceptable maneuvers were noted by the field team. Five pulmonary function parameters were considered: forced vital capacity (FVC), forced expiratory volume at 1 second ($FEV_{1.0}$), the ratio between $FEV_{1.0}$ and FVC, forced expiratory volume at ¾ second ($FEV_{0.75}$), and forced expiratory flow between 25 percent and 75 percent of FVC (FEF_{25-75}). The FVC and $FEV_{1.0}$ measurements were calculated as the mean of the three best efforts that were within 150 ml of the largest measurement (13), and they were corrected to body temperature and pressure saturated (14). FEF_{25-75} was determined from the blow with the largest sum of FVC and $FEV_{1.0}$. A more detailed explanation of the measurement procedure has been provided previously (15).

Logistic regression model for respiratory symptoms

The logistic regression model estimated the effect of the measured level of nitrogen dioxide (annual household average in ppb) while controlling for the effects of city, sex, age at first examination, parental history of bronchitis or emphysema, parental history of asthma, parental college education, single parent family status, and the measured level of respirable particulates in the home (annual average in $\mu g/m^3$). The child's age (7–11 years for the initial questionnaire) was dichotomized into either less than 10 years or 10 or more years of age (27 percent). Parental educational level was positive if the higher education parent living in the child's home had ever attended college (52 percent). Parental chronic obstructive pulmonary disease was positive if a history of bronchitis or emphysema was reported for either of the child's biologic parents (30 percent), while parental asthma was similarly positive for a reported history of asthma (12 percent). The analyses were conducted using SAS PROC LIFEREG with a logistic error distribution (16).

Basic pulmonary function regression model

The analysis of pulmonary function relied on a regression model developed by previous analyses of the Harvard Six Cities Study

children's data (15). Each pulmonary function examination was analyzed separately. The natural logarithm (ln) of pulmonary function was modeled with a separate intercept for each of the six cities and included sex, parental education, parental history of asthma, ln age, ln height, ln weight, and the interaction between sex and ln height. The analyses were conducted using SAS PROC REG (16). In addition to the previous restrictions, the pulmonary function analysis was restricted to children who had complete anthropomorphic and pulmonary function measurements and whose height was 115–155 cm and whose weight was 45–135 lb (20.4–61.2 kg) for the first examination. For the second examination, these measurements were 120–160 cm and 50–150 lb (22.7–68.0 kg), respectively. These restrictions excluded 42 children from the first examination (3.8 percent) and 43 children from the second examination (3.3 percent). Regression analysis prior to the inclusion of the indoor pollution measures identified 10 children whose observed values differed from the predicted values by more than 4 standard errors. These children were excluded from further analyses. After the removal of these outliers, the measured levels of nitrogen dioxide (annual household average in ppb) and respirable particulates (annual average in $\mu g/m^3$) were added to the regression model. The final pulmonary function dataset included 1,053 children for the first examination and 1,175 children for the second examination (figure 1).

RESULTS

Univariate statistics

Table 1 provides descriptive statistics on exposures to indoor air pollutants for the restricted sample of 1,567 children by the presence of a major nitrogen dioxide source in the home for all six cities and by city. Overall, 48 percent of the children lived in homes with a major source of nitrogen dioxide: 83 percent of these children were exposed to a gas cooking stove and 21 percent to a kerosene heater. Homes with a major nitrogen dioxide source had higher proportions of current smokers (62 percent vs. 55 percent), boys (57 percent vs. 49 percent), and single parent families (16 percent vs. 14 percent), but lower proportions of parental chronic obstructive pulmonary disease (28 percent vs. 31 percent), parental asthma (11 percent vs. 13 percent), and one parent with

TABLE 1. Description of exposures by city and presence of a household nitrogen dioxide source (gas cooking stove or kerosene heater): Harvard Six Cities Study, 1983–1988

	Household nitrogen dioxide source	Total cohort (n)	% of children with a nitrogen dioxide source	Gas stoves (n)	Kerosene heaters (n)	Household nitrogen dioxide mean (ppb)			Current smoking household (n)	Annual respirable particulate mean ($\mu g/m^3$)
						Annual	Winter	Summer		
Six cities	No	816				8.6	8.9	9.2	446	31.8
	Yes	751	48	623	156	23.5	28.7	20.9	468	37.8
Watertown, MA	No	63				12.5	10.2	15.9	42	29.8
	Yes	162	72	162	1	27.9	31.5	25.5	118	35.6
Kingston, TN	No	173				6.1	7.3	5.9	73	42.2
	Yes	91	34	3	90	11.0	23.1	5.9	54	48.4
St. Louis, MO	No	69				16.0	15.4	17.7	38	37.3
	Yes	208	75	205	13	31.3	35.5	29.0	139	43.5
Steubenville, OH	No	148				11.4	11.7	12.3	100	33.6
	Yes	93	39	69	29	24.2	31.0	21.3	58	39.4
Portage, WI	No	194				5.7	5.9	6.1	95	24.6
	Yes	110	36	106	10	17.2	20.1	15.5	52	25.2
Topeka, KS	No	169				7.4	8.4	7.5	98	26.4
	Yes	87	34	78	13	16.7	21.4	14.2	47	31.3

a college education (46 percent vs. 57 percent). The annual mean concentration of respirable particles was also higher by 6 $\mu g/m^3$ in the homes with a nitrogen dioxide source.

The household annual average indoor nitrogen dioxide exposure concentration (figure 2) was 14.9 ppb higher for the 751 children living in homes with a major nitrogen dioxide source (mean ± standard error = 23.5 ± 0.4 ppb) than for the 816 children in the nonsource homes (8.6 ± 0.2 ppb). This excess was present in both winter (+19.8 ppb) and in summer (+11.7 ppb). In the homes with a major nitrogen dioxide source, the household average was 7.8 ppb higher in the winter, while in the homes without a major nitrogen dioxide source, the winter measurements were 0.4 ppb lower. Treitman et al. (17) suggested that these seasonal differences reflect decreased winter ventilation and a consequent decrease in the contribution of nitrogen dioxide from external sources. In homes with a major nitrogen dioxide source, the annual average of the two seasonal nitrogen dioxide measurements (figure 3) was higher in the kitchen (28.8 ± 0.6 ppb) than in the activity room (21.6 ± 0.4 ppb) or the child's bedroom (19.8 ± 0.4 ppb). The room-specific indoor nitrogen dioxide measurements were highly correlated with Pearson correlation coefficients greater than 0.90, while the household annual averages for indoor nitrogen dioxide and $PM_{2.5}$ were unrelated. Nitrogen dioxide enters the health effects models as a continuous variable, and the results are presented in this paper as the effect of a 15-ppb increase in the household annual average of the indoor nitrogen dioxide measurements, which is comparable to the crude difference between homes with and without a major nitrogen dioxide source (14.9 ppb).

The household annual indoor nitrogen dioxide averages were modeled using 1,159 children who had complete information on selected household characteristics from the second questionnaire. The final predictors included city, the number of rooms, and indicator variables for gas cooking stove.

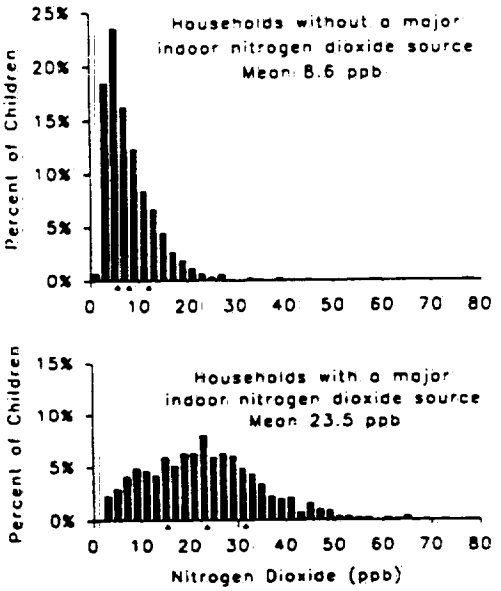

FIGURE 2. Household average nitrogen dioxide measurements by the report of a major indoor nitrogen dioxide source (gas stove or kerosene heater) on the third questionnaire: Harvard Six Cities Study, 1983–1988. Quartiles of the nitrogen dioxide distribution are indicated by triangles below the axis.

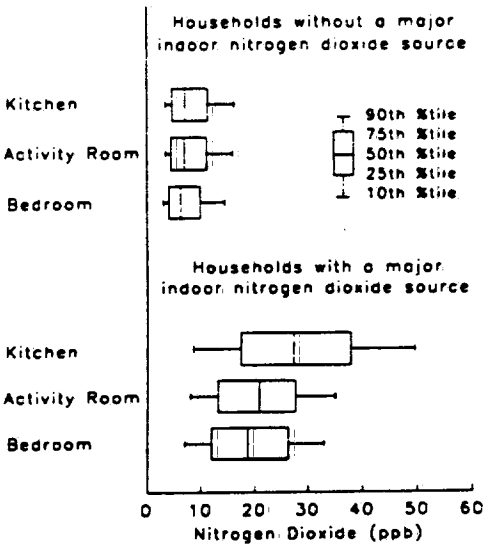

FIGURE 3. Distribution of percentiles for the annual average indoor nitrogen dioxide concentration by room location of the sampler and the report of a major indoor nitrogen dioxide source (gas stove or kerosene heater) on the third questionnaire: Harvard Six Cities Study, 1983–1988.

type of gas fuel, pilot lights, kitchen fan, kerosene space heater, wood stove, and current smoking status. The other variables considered were the use of the cooking stove for heating and the type of fuel used by the main heating system. The final model explained 68 percent of the variation in the measured annual average indoor nitrogen dioxide level and predicted a 17.3-ppb increase in nitrogen dioxide for households using a gas cooking stove with pilot lights. Kerosene space heaters that are typically used only during winter contributed much less (+2.7 ppb) to the annual average nitrogen dioxide level, as did smoking in the home (+1.7 ppb). The nitrogen dioxide measurements were weakly associated with parental education and single parent family status, but not with the child's age or sex or with parental illness.

On the third questionnaire, physician-diagnosed asthma was reported for 6 percent of the children, but asthmatic symptoms were reported twice as frequently: 12 percent for persistent wheeze and 13 percent for shortness of breath with wheeze. The cumulative incidences of chronic cough (8 percent), chronic phlegm (9 percent), and bronchitis (9 percent) were similar. The cumulative incidence of restriction of normal activity for 3 or more days for chest illness (11 percent) was comparable to that for other nonchest illnesses (12 percent). The most common symptoms reported were earache (34 percent) and hay fever (24 percent). The proportion of missing data for each symptom never exceeded 6 percent and was generally 4 percent or less.

Effect of nitrogen dioxide on the annual cumulative incidence of respiratory symptoms

The presence of a major nitrogen dioxide source showed a similar crude association with each of the five lower respiratory symptoms on the third questionnaire (table 2): shortness of breath with wheeze (odds ratio (OR) = 1.24), persistent wheeze (OR = 1.25), chronic cough (OR = 1.29), chronic phlegm (OR = 1.35), and bronchitis (OR = 1.24). Positive associations were not found for asthma, hay fever, earache, or restictions of activity due to either chest illness or other illness. The composite measure of lower respiratory symptoms had a crude odds ratio of 1.38 (95 percent confidence interval (95% CI) 1.05–1.53).

The logistic regression model described earlier was applied to estimate the effect of a 15-ppb difference in indoor nitrogen dioxide on each of the symptoms. The adjusted odds ratios were similar to the crude relative risks associated with the presence of a major nitrogen dioxide source. The composite indicator of lower respiratory symptoms had a statistically significant association with indoor nitrogen dioxide. When expressed as the effect of a 15-ppb increase in the household annual average of the nitrogen dioxide measurements in the child's home, the adjusted odds ratio was 1.40 (95 percent CI 1.14–1.72).

Over the 3 years of questionnaires, the cumulative incidence rates of lower respiratory symptoms increased among children in homes with a major nitrogen dioxide source: 22 percent in the first, 24 percent in the second, and 29 percent in the third. Rates were stable for the children living in nonsource homes: 21 percent, 21 percent, and 23 percent. The crude relative odds of lower respiratory symptoms increased steadily over the three questionnaires (1.05, 1.17, and 1.38), as did the adjusted odds ratios (0.90, 1.21, and 1.40).

When the third questionnaire was analyzed separately by sex, an increased effect of nitrogen dioxide was seen among the girls (OR = 1.68, 95 percent CI 1.30–2.19) compared with boys (OR = 1.16, 95 percent CI 0.89–1.51). Similarly, the nitrogen dioxide effect appears to be stronger among children with current domestic exposure to passive cigarette smoke (OR = 1.48, 95 percent CI 1.19–1.84) compared with those in nonsmoking homes (OR = 1.22, 95 percent CI 0.89–1.66).

When the analysis was repeated separately for each city (table 3), the estimates of the effect of a 15-ppb increase in nitrogen dioxide on lower respiratory symptoms were

TABLE 2. Annual cumulative incidences and crude odds ratios (ORs) associated with a major indoor nitrogen dioxide source (gas stove or kerosene heater) and the adjusted odds ratios and 95% confidence intervals (95% CIs) associated with a 15-ppb increase in the annual average indoor nitrogen dioxide exposure by symptom: Harvard Six Cities Study, 1983–1988

	Effect of nitrogen dioxide source category			Effect of a 15 ppb difference in nitrogen dioxide, adjusted*	
	Cumulative incidence (%)		Crude OR	OR	95% CI
	No source	Source			
Shortness of breath	11.5	13.9	1.24	1.23	0.93–1.61
Chronic wheeze	11.3	13.8	1.25	1.16	0.89–1.52
Chronic cough	7.6	9.5	1.29	1.18	0.87–1.60
Chronic phlegm	8.2	10.7	1.35	1.25	0.94–1.66
Bronchitis	7.8	9.4	1.24	1.05	0.75–1.47
Lower respiratory symptoms	22.8	29.0	1.38	1.40	1.14–1.72
Asthma	7.1	5.4	0.75	0.91	0.60–1.36
Hay fever	24.0	24.7	1.04	0.98	0.79–1.22
Earache	34.5	33.0	0.94	1.09	0.90–1.32
Chest illness	10.5	11.0	1.06	1.10	0.83–1.46
Other illness	12.3	12.5	1.02	1.06	0.81–1.40

* Odds ratios adjusted for city, sex, age, parental history of bronchitis or emphysema, parental history of asthma, parental college education, single parent family status, and the measured levels of respirable particulates in the home.

TABLE 3. Annual cumulative incidences of lower respiratory symptoms and crude odds ratios (ORs) associated with a major indoor nitrogen dioxide source (gas stove or kerosene heater) and the adjusted odds ratios and 95% confidence intervals (95% CIs) associated with a 15-ppb increase in the annual average indoor nitrogen dioxide exposure by city: Harvard Six Cities Study, 1983–1988

	Effect of nitrogen dioxide source category			Effect of a 15 ppb difference in nitrogen dioxide, adjusted*	
	Cumulative incidence (%)		Crude OR	OR	95% CI
	No source	Source			
Watertown, MA	14.3	15.5	1.10	1.27	0.59–2.72
Kingston, TN	22.4	42.9	2.60	1.32	0.63–2.77
St. Louis, MO	27.8	23.2	0.79	1.27	0.88–1.85
Steubenville, OH	29.0	39.0	1.57	1.44	0.97–2.13
Portage, WI	17.7	26.9	1.71	1.86	1.13–3.04
Topeka, KS	24.7	34.3	1.59	1.26	0.72–2.20

* Odds ratios adjusted for city, sex, age, parental history of bronchitis or emphysema, parental history of asthma, parental college education, single parent family status, and the measured levels of respirable particulates in the home.

nearly equal in spite of a considerable variation in the city-specific prevalence of major nitrogen dioxide sources as shown in table 1.

A consistent pattern also was found when the analysis was repeated separately for each source category (table 4). For this table, the classification of households was based on any mention of a major indoor nitrogen dioxide source on either the second or the third questionnaire, that is, before or after the indoor monitoring. The estimated effect of a 15-ppb increase in the annual average indoor nitrogen dioxide exposure was slightly lower among the 495 children from gas stove homes compared with the 181 children from homes with kerosene heaters. The estimated nitrogen dioxide effect was slightly lower among the 630 children from homes without any report of a major nitrogen dioxide source on either questionnaire. The nitrogen dioxide effect estimate for non-source homes was dominated by a single home's high nitrogen dioxide level (58.3 ppb). Deleting this observation reduced the maximum value of the average annual in-

door nitrogen dioxide concentration to 35.6 ppb and reduced the estimated odds ratio for nonsource homes to OR = 1.01 (95 percent CI 0.44–2.32).

To check the modeling of nitrogen dioxide as a continuous variable, nitrogen dioxide measurements were collapsed into four ordered exposure categories of approximately equal size (table 5). The mean nitrogen dioxide levels varied from 3.7 ppb in the lower exposure category to 31 ppb in the upper exposure category, while the presence of a major household nitrogen dioxide source varied from 9 percent to 93 percent. The relative odds for lower respiratory symptoms increased monotonically with the mean nitrogen dioxide level.

Effect of nitrogen dioxide on pulmonary function measurements

The pulmonary function measures were conducted in conjunction with the first two questionnaires and preceded the indoor pollutant measurements. No pulmonary function measurements were made in conjunction with the third questionnaire following the indoor monitoring. For an additional 15 ppb of nitrogen dioxide, the only association which reached statistical significance was an increase in $FEV_{1.0}/FVC$ among boys ($p < 0.04$). There was no indication that nitrogen dioxide exposure was associated consistently with a reduction in any of the pulmonary function measures (table 6).

DISCUSSION

Previous studies

Unvented gas household appliances have been reported in US and European studies to be associated with increased respiratory symptoms in children. In a study of 5,758 English children aged 6–11 years, Melia et al. (18) reported that gas cooking stoves were associated with the increased prevalence of six respiratory symptoms among boys

TABLE 4. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) associated with a 15-ppb increase in the annual average indoor nitrogen dioxide exposure by major indoor nitrogen dioxide source category as reported on a questionnaire either before or after indoor air sampling: Harvard Six Cities Study, 1983–1988

Nitrogen dioxide source category	No. of children	Nitrogen dioxide level (ppb)		Adjusted*	
		Range	Mean	OR	95% CI
Gas stove	495	2.1–78.2	24.5	1.37	1.02–1.84
Kerosene heater	181	2.6–69.3	13.2	1.45	0.82–2.56
No reported major indoor source	630	1.7–58.3	7.5	1.23	0.62–2.47

* Odds ratios adjusted for city, sex, age, parental history of bronchitis or emphysema, parental history of asthma, parental college education, single parent family status, and the measured levels of respirable particulates in the home.

TABLE 5. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) associated with ordered indoor nitrogen dioxide exposure categories on the annual cumulative incidence of lower respiratory symptoms: Harvard Six Cities Study, 1983–1988

Nitrogen dioxide level (ppb)		Nitrogen dioxide source (%)	No. of children	Cumulative incidence (%)	Adjusted*	
Range	Mean				OR	95% CI
0–4.9	3.7	9	263	22.8	1.00	
5–9.9	7.3	20	360	24.2	1.06	0.71–1.58
10–19.9	14.4	50	317	27.1	1.36	0.89–2.08
20–78.2	31.0	93	346	27.8	1.65	1.03–2.63

* Odds ratios adjusted for city, sex, age, parental history of bronchitis or emphysema, parental history of asthma, parental college education, single parent family status, and the measured levels of respirable particulates in the home.

TABLE 6. Percentage of change in selected pulmonary function measurements and 95% confidence intervals (95% CIs) associated with a 15-ppb increase in the annual average indoor nitrogen dioxide exposure by examination and sex: Harvard Six Cities Study, 1983–1988

	First examination		Second examination	
	% of change*	95% CI	% of change	95% CI
Males				
FVC†	−0.7	−2.0 to +0.6	−0.4	−1.6 to +0.8
$FEV_{1.0}$†	+0.1	−1.3 to +1.5	−0.1	−1.5 to +1.3
$FEV_{1.0}$/FVC	+0.8	+0.0 to +1.6	+0.3	−0.5 to +1.1
$FEV_{0.75}$†	+0.1	−1.4 to +1.5	−0.1	−1.6 to +1.3
$FEF_{25-75\%}$†	+1.8	−1.1 to +4.6	+0.7	−2.2 to +3.5
$FEV_{25-75\%}$/FVC	+2.5	−0.3 to +5.2	+1.1	−1.7 to +3.8
Females				
FVC	+0.7	−0.8 to +2.2	−0.6	−2.0 to +0.7
$FEV_{1.0}$	+0.9	−0.6 to +2.4	−0.2	−1.6 to +1.1
$FEV_{1.0}$/FVC	+0.2	−0.6 to +1.0	+0.4	−0.3 to +1.1
$FEV_{0.75}$	+0.7	−0.9 to +2.3	−0.3	−1.7 to +1.1
$FEF_{25-75\%}$	+0.3	−3.0 to +3.4	+0.1	−2.7 to +2.8
$FEV_{25-75\%}$/FVC	−0.5	−3.7 to +2.7	+0.7	−2.1 to +3.4

* Percentage of change adjusted for city, parental history of asthma, parental college education, in age, in weight, and in height.
† FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 second; $FEV_{0.75}$, forced expiratory volume in three-fourths of a second; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of FVC; ln, natural logarithm.

(OR = 1.27, 95 percent CI 1.08–1.50) and girls (OR = 1.39, 95 percent CI 1.16–1.65), after controlling for age and social class. After controlling for 28 geographic areas, the association remained significant for girls ($p < 0.05$), but not for boys ($p \sim 0.30$). Subsequent studies by Keller et al. (19) of 441 Columbus, Ohio, families and by Schenker et al. (20) of 4,071 Pennsylvania children failed to detect any significant associations between gas stoves and the incidence or prevalence of respiratory symptoms. In fact, Keller and coworkers found a protective effect for gas stoves that may have been an artifact of controlling for the child's prior illness history. If chronic exposure to nitrogen dioxide is a risk factor for early childhood illnesses, controlling for the child's illness history will substantially reduce the estimated effect of current nitrogen dioxide exposures. Dodge (21) found a very large excess prevalence (OR = 2.2, $p < 0.05$) of cough associated with gas stoves in a study of 676 children in three Arizona communities.

Gas stoves have shown an association with respiratory symptoms among an earlier cohort of children participating in the Harvard Six Cities Study. In a preliminary report on 8,120 children, Speizer et al. (22, 23) found that gas cooking stoves were significantly associated with respiratory illness prior to age 2 (OR = 1.12, 95 percent CI 1.00–1.26). In a follow-up analysis of a larger cohort of 10,106 of these children, Ware et al. (3) reported that a similar association was found between gas stoves and respiratory illness prior to age 2 (OR = 1.13, 95 percent CI 0.99–1.28), which was slightly reduced by an adjustment for parental education (OR = 1.11, 95 percent CI 0.97–1.27). No significant associations were found for any reports of respiratory symptoms in the previous year, including chronic cough, persistent wheeze, and bronchitis. For a second sample of 6,273 children in the six cities from which the participants in the present study were selected, Dockery et al. (4) reported that physician-diagnosed respiratory illness prior to age 2 was significantly associated with gas cooking stoves with pilot lights (OR = 1.22, 95 percent CI 1.02–1.47) and marginally associated with kerosene heaters (OR = 1.11, 95 percent CI 0.89–1.37). No associations were found with individual respiratory symptoms in the previous year as reported on the first questionnaire. Neither gas stoves not kerosene heat-

ers were associated with differences in pulmonary function measurements. Ekwo et al. (24) also have found an increased prevalence (OR = 2.4, 95 percent CI 1.4–4.1) of hospitalization for respiratory illness before age 2 among 1,138 Iowa City children.

Measured levels of indoor nitrogen dioxide also were reported to have an association with respiratory symptoms in children. Florey et al. (25) reported that the prevalence of a combined indicator of respiratory symptoms was not associated with kitchen nitrogen dioxide levels among 428 children in gas cooking homes, but was associated with bedroom nitrogen dioxide levels among a subsample of 80 children ($p < 0.10$). In a 1982 follow-up study of children living in 183 gas cooking homes, Melia et al. (26) reported that living room nitrogen dioxide measurements were significantly associated with the prevalence of respiratory conditions at the 90 percent confidence level, but bedroom nitrogen dioxide measurements showed no significant association. In a 1987 study of 121 children under the age of 13 years, Berwick et al. (27) reported an association between living room nitrogen dioxide measurements over 16 ppb and increased reporting of eight lower respiratory symptoms among children under 7 years, but not among children 7 years and older after controlling for socioeconomic status and history of respiratory illness. As with the study by Keller et al., Berwick's control for prior respiratory illnesses may have weakened any association with nitrogen dioxide exposure.

In a 1990 study of 775 Dutch children aged 6–12 years, Dijkstra et al. (28) found no association between mean indoor nitrogen dioxide concentrations and a combined indicator of one or more of three lower respiratory symptoms: chronic cough, any mention of wheeze, and attacks of shortness of breath with wheeze. The nitrogen dioxide measurements were collected over 1 week in January, compared with the 2 weeks of measurements in both the winter and summer seasons used for the present study. The 1-week winter samples of Dijkstra et al. provide a less reliable estimate of each child's exposure to nitrogen dioxide over the entire year. The range of exposures was somewhat smaller with only 79 (10 percent) children (eight of whom had one or more symptoms) who lived in homes with a 1-week average winter measurement more than 32 ppb of nitrogen dioxide, compared with 195 (15 percent) of the 1,286 children in the present study with a 2-week average winter concentration above 32 ppb. Nevertheless, there is no clear explanation at this time for the lack of association in this study.

Pulmonary function measurements have not shown a consistent association with either gas stoves or with direct measurements of nitrogen dioxide exposure. Hasselblad et al. (29) reported a decline in pulmonary function among 3,000 girls aged 9 through 13 years (−1.1 percent $FEV_{0.5}$), but a slight increase among 3,552 boys aged 9 through 13 years (+0.3 percent $FEV_{0.5}$). In a longitudinal analysis of 7,834 children in the Harvard Six Cities Study cohort, Berkey et al. (30) reported slight declines in both FVC (−0.55 percent, 95 percent CI −1.16 percent to +0.05 percent) and $FEV_{1.0}$ (−0.41 percent, 95 percent CI −1.03 percent to +0.02 percent) for both sexes combined. Slightly greater than predicted levels of pulmonary function were found in the study of Vedal et al. (31) of 1,631 children living in gas stove homes (+0.1 percent $FEF_{25-75\%}$). In an English study of 485 children, Florey et al. (25) found no association between kitchen nitrogen dioxide measurements and pulmonary flow measurements after adjustment for age, height, weight, and sex, although girls in gas cooking homes had significantly higher values of peak expiratory flow and $FEF_{25-75\%}$.

Present study

The present study is in substantial agreement with these previous studies in finding an association between measured levels of indoor nitrogen dioxide and the cumulative incidence of a combined indicator of respiratory symptoms. In this study, lower respi-

ratory symptoms were linearly associated with indoor nitrogen dioxide with an odds ratio of 1.40 for an increase in nitrogen dioxide equivalent to that for a gas stove. This is similar in magnitude to the previously reported effect of passive smoke exposure. For example, Ware et al. (3) report a relative odds of 1.23 for the association between maternal smoking and an index of lower respiratory illness in an earlier cohort in these cities. The association is stronger among girls and among children living in smoking homes, but the effect is still present among boys and among children living in nonsmoking homes. Melia et al. (26) found a stronger association among girls between gas stove exposure and respiratory symptoms. The lack of a significant adverse effect on pulmonary function is in agreement with the results of Berkey et al. (30) and Vedal et al. (31). These findings appear to indicate that either the increased prevalence of respiratory symptoms due to nitrogen dioxide exposure does not lead to any impairment of pulmonary function or the impairment of pulmonary function is a delayed or rare result of nitrogen dioxide exposure, but they are in agreement with the lack of a consistent finding of reduced pulmonary function among children with viral bronchiolitis (32), a condition which is similar to the toxic bronchiolitis that may be produced by acute nitrogen dioxide poisoning.

The nitrogen dioxide effect is remarkably consistent when the analysis is repeated separately for each city and each nitrogen dioxide source category (tables 3 and 4). Such consistency implies that other factors, such as climate and social class that may be associated with city or source category, do not strongly confound the nitrogen dioxide effect estimate. In particular, this consistency is striking, given the wide variation in the actual nitrogen dioxide exposure levels across city and source categories. This suggests that nitrogen dioxide is a common linkage in the observed health effects, even though a more toxic by-product of indoor nitrogen dioxide may be the primary irritant. Pitts et al. (33) have suggested that nitrogen dioxide reacts with interior surfaces to produce nitrous acid. In either case, indoor nitrogen dioxide is specifically implicated, whether directly affecting symptom reporting or indirectly through the production of nitrous acid.

Alternatively, selective inclusion or exclusion of participants is a potential source of bias due to the loss of children over the 3 years of the study. Complete measurements for indoor pollutants were not obtained for all of the households initially selected for inclusion in the indoor air quality monitoring study, but these sampling losses were not associated with differences in household source characteristics. Children were also lost to follow-up because of failure to obtain all three questionnaires. In large part, this attrition was because of school busing in St. Louis and the poor response to a mail distribution of the third questionnaire in Watertown. Neither of these is likely to have been strongly associated with nitrogen dioxide exposure. The overall symptom prevalence rate increased over the course of the study, which may be due to either parents with asymptomatic children losing interest in participating in the study or parents who did not accurately complete the initial symptom questionnaires withdrawing from the sample in subsequent years. In any case, the two cities with the highest retention rates, Steubenville (88 percent) and Portage (99 percent), had the highest city-specific estimates for the association of nitrogen dioxide with lower respiratory symptoms.

A second alternative explanation for these findings is that other variables associated with both nitrogen dioxide exposure and respiratory symptom reporting, i.e., confounders, may be producing a spurious association. The strongest confounder in this study was socioeconomic status, and controlling for this and other potential confounders in the model actually increases the association from a crude odds ratio of 1.38 to an adjusted odds ratio of 1.40. Family size, the presence of younger siblings, and the number of persons per room were found to have no significant effect when considered for inclusion in the model. Neither excluding parental illness from the model nor in-

cluding an indicator for maternal smoking during pregnancy altered the adjusted odds ratio.

Home wetness was also considered as a potential confounder. Goldstein et al. (34) reported that unvented gas appliances raise humidity and cause surface condensation in the home that may act independently to increase respiratory symptoms. In a cohort of 4,625 children from which the children in the current study were selected, Brunekreef et al. (35) reported that home dampness indicators were significantly associated with increased reporting of respiratory symptoms. In the indoor air-monitoring sample, home dampness indicators were associated with the combined indicator of lower respiratory symptoms, but only weakly associated with nitrogen dioxide. Controlling for the effects of home dampness did not modify the association of lower respiratory symptoms with the indoor nitrogen dioxide concentrations.

The misclassification of children with regard to either exposure or symptoms also may have introduced a bias. As the symptom measurements become more remote in time from the indoor monitoring, the observed effect of nitrogen dioxide appears to diminish. This may be due to either a systematic bias or may represent a real temporal variability of the results. The increased rate of symptom reporting over the three questionnaires by parents with a major nitrogen dioxide source could be explained by overreporting as these parents became aware of the hypothesized association of respiratory illness and gas stoves. However, such a bias would not explain the dose-response association found with level of nitrogen dioxide nor the consistent associations found when the children were considered separately by source class. An alternative explanation for this trend is that there was increasing nondifferential misclassification of exposure, i.e., the indoor nitrogen dioxide concentration, as the questionnaires become more remote in time from the indoor measurements during the final year of the study.

For any exposure assessment scheme, the highest observed levels are produced by a process that involves both the average exposure level in the home and the chance occurrence of unusually high exposure events. As the number of samples and the duration of the sampling period are increased, chance deviations in the nitrogen dioxide level make less of a contribution to the estimated annual average nitrogen dioxide exposure level. In this study, the collection of samples over a 2-week period in both the winter and summer provides a better estimate of each child's long-term average nitrogen dioxide exposure than samples collected over a single winter week. By reducing the contribution of chance events to the exposure assessment, repeated measurements over an extended period reduce the nondifferential misclassification of children with regard to exposure and, thus, the bias toward the null which such misclassification generally introduces into the effect estimate.

Questionnaire responses are also subject to recall biases and nondifferential misclassification. Recall bias is also suggested by the higher rates of the child's respiratory symptoms by parents with asthma or chronic obstructive pulmonary disease. However, these parental illnesses were not correlated with the nitrogen dioxide measurements and, thus, cannot bias the associations with nitrogen dioxide. Even with the use of a standardized questionnaire of respiratory symptoms, parents apply different interpretations of the symptom questions in reporting their children's symptoms. For example, the parent's choice between reporting chronic cough, chronic phlegm, and/or bronchitis may be related to factors other than their child's actual symptom history. Thus, it is appropriate to consider not only specific symptoms but also composite measures that combine data from correlated symptoms with related physiologic bases. In this study, the lower respiratory symptom complex combines data from several correlated symptoms that are characteristic of lower rather than upper respiratory tract illnesses, reducing misclassification between symptoms.

This study provides evidence that nitrogen dioxide concentrations in the home are as-

sociated with increased parental reporting of lower respiratory symptoms in children. However, no permanent changes in lung airways associated with nitrogen dioxide were detected with standard pulmonary function examinations. These findings are consistent with reports from previous studies that have used indicators of indoor nitrogen dioxide sources other than direct measurements of indoor concentrations. The monotonic increase in the reporting of lower respiratory symptoms with the ordered nitrogen dioxide exposure categories (table 5) implies that nitrogen dioxide has adverse health effects at levels below the current ambient outdoor standard of 53-ppb annual mean. Since the specific toxic agent may be a product of subsequent reaction of nitrogen dioxide on indoor surfaces to produce acid gases, future investigations of the indoor chemistry of nitrogen dioxide may suggest alternative mitigation techniques. However, this study suggests that a direct reduction of indoor nitrogen dioxide exposures would have health benefits: i.e., the relative odds of lower respiratory symptoms would drop by 29 percent for each 15-ppb decrease in the annual mean indoor nitrogen dioxide concentration. Such exposure reductions could come through the control of indoor nitrogen dioxide sources, through the removal of nitrogen dioxide from outdoor air infiltrating into the home, and through the reduction of ambient nitrogen dioxide concentrations.

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APPENDIX

Imputation of indoor air quality values for a single missing season

For the kitchen measurements of nitrogen dioxide, 1,358 (87 percent) of the restricted cohort of 1,567 children had at least one valid measurement in each season, and 768 (57 percent) of these had two valid measurements in one or both seasons. An additional 196 children had valid measurements of kitchen nitrogen dioxide for one season but had no valid measurements in the other season: 34 children in the winter and 162 children in the summer. The other sampling locations had similar patterns of missing values. For respirable particulates, 1,318 of the children had at least one valid measurement in each season, and 1,277 of these had two valid measurements in one or both seasons. An additional 222 children had valid measurements of respirable particulates for one season but had no valid measurements in the other season: 72 children in the winter and 150 children in the summer. The increase in missing values during the summer was generally due to difficulties in scheduling the sampling with respect to family vacations.

The replicate measurement of each indoor pollutant in both seasons for the majority of the children's homes permits the imputation of values for homes with no valid measurements for a single season. The algorithm for computing these imputed values comprises the following steps.

1) For the sample of all individuals ($i = 1$ to n_j, $n_j < n_{j'}$) with two observations in a single season (j), calculate an estimate of the between-week variance for each season (j and j'):

$$s^2_{wn(j)} = \sum \tfrac{1}{2} (X_{i,j1} - X_{i,j2})^2/(n_j - 1)$$

2) For each season (j and j') and each individual ($i = 1$ to $n_{j'}$, $n_{j'} > n_j$) with at least one

observation in that season, calculate a seasonal mean and a seasonal between-week variance:

$$\text{If two observations: } \bar{X}_{ij} = (X_{ij1} + X_{ij2})/2$$

$$\phi^2_{ij} = (X_{ij1} - X_{ij2})^2/4$$

$$\text{If one observation: } \bar{X}_{ij} = X_{ij1}$$

$$\phi^2_{ij} = s^2_{\text{mat}\,ij}$$

3) For the entire sample of all individuals ($i = 1$ to n^*, $n_j > n^* > n_{j'}$) with at least one observation in both seasons, calculate a grand mean for each season (j and j'):

$$\bar{X}_j = \sum \bar{X}_{ij}/n^*$$

4) For the entire sample of all individuals ($i = 1$ to n^*, $n_j > n^* > n_{j'}$) with at least one observation in both seasons, calculate the slope and intercept of a prediction equation that will impute the seasonal mean for a season with no valid observations from the seasonal mean of a season with one or more valid observations (j and j'):

$$\text{Slope: } \hat{\gamma}_{1j} = \frac{\sum (\bar{X}_{ij} - \bar{X}_j)(\bar{X}_{ij'} - \bar{X}_{j'})}{\sum [(\bar{X}_{ij} - \bar{X}_j)^2 - \phi^2_{ij}]}$$

$$\text{Intercept: } \hat{\gamma}_{0j} = \bar{X}_j - \hat{\gamma}_{1j}\bar{X}_{j'}$$

5) For the entire sample of all individuals ($i = 1$ to n^*, $n_j > n^* > n'_{j'}$) with at least one observation in both seasons, calculate the season error variance for each season (j and j'):

$$\hat{\sigma}^2_j = \frac{\sum [(\bar{X}_{ij} - \bar{X}_j) - \gamma_{1j}(\bar{X}_{ij'} - \bar{X}_{j'})]^2 - \gamma^2_{1j}\phi^2_{ij'}}{n^* - 2}$$

6) For each individual ($i = 1$ to n^0_j) with no valid observations in a single season (j), but at least one observation in the other season (j'), impute a mean and a between-week variance for the missing season (j):

$$\bar{X}_{ij} = (\bar{X}_{ij'} - \hat{\gamma}_{0j})/\hat{\gamma}_{1j}$$

$$\phi^2_{ij} = (\phi^2_{ij'} + \hat{\sigma}^2_j)/\hat{\gamma}^2_{1j}$$

7) For each individual ($i = 1$ to n, $n > n_j$) with at least one observation in either season, calculate the annual mean:

$$\bar{X}_i = (\bar{X}_{ij} + \bar{X}_{ij'})/2$$

8) For each individual ($i = 1$ to n^*, $n > n^* > n_j$) with at least one observation in both seasons, calculate an annual variance:

$$\psi^2_i = (\phi^2_{i1} + \phi^2_{i2})/4$$

For each individual ($i = 1$ to $n^{(1)}_j$) with no valid observations in a single season (j), but at least one observation in the other season (j'), impute an annual variance:

$$\psi^2_i = \left[\phi^2_{ij} + \left(1 + \frac{2}{\gamma_{1j}}\phi^2_{ij'}\right)\right]/4$$